



# Broad-based genomic sequencing in advanced non-small cell lung cancer in the dock

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The recently published study of Presley and colleagues (1) aimed to ascertain if there is an association between broad-based genomic sequencing (defined as multigene Next-Generation Sequencing panels of 30 or more genes) and better survival in patients with advanced non-small cell lung cancer (NSCLC). For this purpose, the authors retrospectively analyzed data obtained from medical records of a large cohort of patients (n=5,688) with NSCLC from January 2011 to July 2016, treated in 191 community oncology practices across the United States. Overall, broad-based genomic sequencing was performed for 875 patients (15.4%) and routine genomic testing (testing of *EGFR/ALK* only) for 4,813 patients (84.6%). These two groups were compared for two parameters: the 12-month mortality using an instrumental variable approach and the overall survival with a propensity score-matched survival analysis. According to these analyses, the authors found no significant association between broad-based genomic sequencing and 12-month mortality [predicted probability of death: 41.1% for broad-based genomic sequencing *vs.* 44.4% for routine testing; difference -3.6%, (95% CI, -18.4% to 11.1%)] or overall deaths [42.0% *vs.* 45.1%; hazard ratio, 0.92 (95% CI, 0.73–1.11)], despite the unadjusted Kaplan-Meier survival analysis showing better survival with broad genomic sequencing [hazard ratio 0.69 (95% CI, 0.62–0.77); log-rank  $P < 0.001$ ]. The authors concluded that the use of broad-based genomic sequencing for advanced NSCLC

in the community setting is not independently associated with a survival advantage. The study conducted by Presley *et al.* (1) presented interesting data about the use of broad genomic approach as compared to routine genomic testing across different community oncology practices and among a large cohort of patients with NSCLC. However, some considerations are needed regarding the usefulness of multi-gene approach and the potential clinical benefit of targeted treatment.

First, as the authors reported, at the time of the study routine testing for *EGFR/ALK* only was considered the standard-of-care for patients with advanced NSCLC. However, the recently updated guidelines regarding the molecular testing in patients with advanced lung cancer, recommended a wider panel of genes to be tested in order to drive personalized therapy (2,3) including *ROS1* and *BRAF* evaluations as stand-alone tests and *RET*, *ERBB2 (HER2)*, *KRAS*, and *MET* analyses as part of larger panels (2). Moreover, the number of biomarkers to be tested may rise rapidly as data are emerging about the oncogenic role of additional molecular aberrations that could be efficacy targeted by new drugs (e.g., *NTRK1/2/3* fusion genes or *NF1* mutations) (4,5). In our experience, using a multi-gene panel we could identify an overall rate of 32.6–39.8% of patients with advanced NSCLC harboring alterations targetable by therapies in a clinical setting or clinical trials (6,7). This prevalence is also confirmed by the

study of Presley (1) that reported 18% and 3.7% of *EGFR*-mutated and *ALK*-rearranged cases respectively and identified additional alterations in *ROS1*, *MET*, *BRAF*, *ERBB2*, *NTRK1-3*, and *RET* in at least 125 patients (14.3%) using broad-based genomic sequencing. However, only a small number of these patients received a broad-based genomic sequencing directed targeted treatment (n=36), leading to the conclusion that this broad sequencing approach may not currently improve survival (1). Undoubtedly, no survival advantage could be expected if the alteration is identified but the patient is not actively treated. This observation is valid regardless of the type of target treatment adopted, still fitting for *EGFR* or *ALK* target therapies (8,9). Therefore, the clinical benefit could be achieved only if the broad-based genomic sequencing is combined with a broad targeted drug availability.

Second, a multi-gene approach may add and not decrease information to data obtained from single-gene routine testing only. As reported by Presley (1), there was a high concordance (98–99.1%) between 399 *EGFR* and 330 *ALK* tests performed in patients who received both broad-based genomic sequencing testing and single-gene testing. Beside, upfront multi-gene panels could be useful in terms of turnaround time, cost-effectiveness and tissue management (10,11). Nowadays, Next Generation Sequencing (NGS) panels require a small quantity of input DNA and allow to simultaneously evaluate a large number of genes and different type of alterations, including single nucleotide variants, insertion or deletions, copy number variation, and fusion genes (12). On the other hand, serial testing of single genes may expand turnaround time and tissue requirement. This is especially true for advanced NSCLC-testing, where the samples are often endobronchial ultrasound biopsies, lung biopsies or cytological samples with limited amount of material (13). Moreover, a multi-gene panel approach could be useful not only at diagnosis but also in the monitoring of therapy response for the identification of acquired resistance mechanisms. Indeed, acquired resistance may be related not only to “on-target” mechanisms (e.g., secondary acquired T790M mutation in *EGFR*) but also to “off-target” mechanisms including bypass or downstream signaling pathway activation (e.g., *MET* alterations in *EGFR*-mutated NSCLC treated with EGFR inhibitors) (14).

Third, a multi-gene comprehensive analysis could be useful for clinical decision making not only about specific targeted therapy but also about different therapy regimens, including immunotherapy. In the last years, PD-1/PD-

L1 inhibitors have been rapidly emerging as a therapeutic option for patients with advanced NSCLC (15-17). In the study of Presley *et al.* (1) there was a significant association between the selection of immunotherapy as 1<sup>st</sup> or 2<sup>nd</sup> line treatment and the receipt of broad-based genomic sequencing (P<0.001). Even if these data were not discussed and the molecular profile of patients receiving immunotherapy was not reported, immunotherapy within the first 4<sup>th</sup> lines of treatment was significantly associated with improved survival [adjusted hazard ratio 0.41 (95% CI, 0.36–0.47), P<0.001]. Tumors with *ROS1* or *ALK* rearrangement or *EGFR* mutation frequently showed a high expression of PD-L1 (18,19); however, the presence of these driver alterations has been recently associated with low response to PD-1/PD-L1 inhibitors (20). Prospective studies are thus warranted to evaluate the efficacy of immunotherapy in such patients. However, the exclusion of driver mutations using a broad-based sequencing approach may represent another important information provided to the clinicians to drive therapy decision. Moreover, although is still highly debated, tumor mutational burden may become an additional predictive biomarker for immunotherapy (21). In this scenario, only large (>1 Mb tumor coding genome covered) multi-gene NGS panels could be adopted (22).

In conclusion, the study conducted by Presley and colleagues provides important insights into the prevalence of broad-based genomic sequencing in the community oncology setting. The authors concluded that this sequencing approach might not currently offer a survival advantage in patients with NSCLC. However, assessing at the same time different individual diagnostic and prognostic risk factors as well as druggable alterations represents the main goal of the precision medicine (23). Indeed, the broad-based genomic sequencing may reveal its clinical utility only into the context of a multidisciplinary team setting, where clinical requests and molecular results could be joined and discussed to improve the therapeutic opportunity for each patient (24).

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## Footnote

*Conflicts of Interest:* The authors have no conflicts of interest to declare.

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